IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
TO THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of	:	William S. Brusilow
Serial No.	:	10/758,415
For	:	TREATMENT OF POLYGLUTAMINE DISORDERS CAUSED BY EXPANDING GENOMIC CAG NUCLEOTIDES
Filed	:	January 16, 2004
TC/A.U.	:	1614
Examiner	:	Zohreh Vakili
Docket No.	:	2930-109
Customer No.	:	6449
Confirmation No.	:	5654

Commissioner for Patents
P.O. Box 1450
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May 18, 2010

APPELLANT'S APPEAL BRIEF UNDER 37 C.F.R. §41.37

Sir:

The following comprises the Patent Owner's Brief on Appeal from the Office Action dated February 18, 2010, in which claims 1-5, 10-11 and 21, were finally rejected. A Notice of Appeal is being filed with this brief. This Appeal Brief is accompanied by the required Appeal fee set forth in 37 C.F.R. § 41.20(b)(2), and is being timely filed on May 18, 2010.

I.

REAL PARTY IN INTEREST

The owner of the above-referenced patent and the real party in interest in this appeal is Odessa Pharma, Chevy Chase, Maryland, USA.

II.

RELATED APPEALS AND INTERFERENCES

The Patent Owner is unaware of any other appeals or interferences related to the subject matter of this appeal.

III.

STATUS OF CLAIMS

The rejection of claims 1-5, 10-11 and 21 is being appealed. Claims 1 and 21 are independent with claims 2-5 and 10-11 depending directly from claim 1. Claims 6-9 and 12-20 are withdrawn. No claims are allowed. The appealed claims are reproduced in the Appendix attached hereto.

IV.

STATUS OF AMENDMENTS

No amendments were made in response to the Office Action mailed June 11, 2009 and no amendments are being made in response to the Office Action dated February 18, 2010. Therefore, it is believed that all amendments have been entered.

V.
SUMMARY OF THE CLAIMED SUBJECT MATTER

A number of neurodegenerative polyglutamine diseases are characterized by expanded genomic CAG sequences resulting in the synthesis and accumulation of polyglutamine tracts in brain proteins of unknown function that are responsible for the neurologic problem. The CAG codon is translated into glutamine (Q). Proteins with expanded polyglutamine domains aggregate and aggregation is a pathologic hallmark of the polyglutamine repeat diseases (page 1, lines 16-23). These polyglutamine length-dependent properties may arise from the ability of long polyglutamine domains to adopt unique three-dimensional conformations and serve to confer the disease proteins with a pathologic gain-of-function (page 2, lines 1-5). All diseases in the CAG repeat family show genetic anticipation, meaning the disease usually appears at an earlier age and increases in severity with each generation. Genetic anticipation is linked to increasing numbers of CAG repeats, which result from expansion of the unstable CAG sequence when reproductive cells divide to form eggs and sperm. In general, neurodegenerative disorders are progressive (i.e., their symptoms are not apparent until months or more commonly years after the disease has begun), and caused by an initial reduction of neuronal function, followed by a complete loss of function upon neuronal death (page 2, lines 7-14).

Currently, physicians prescribe a number of medications to help control emotional and movement problems associated with polyglutamine disorders caused by

expanded genomic CAG nucleotides. Such medications include antipsychotic drugs, such as haloperidol, or other drugs, such as clonazepam, to alleviate choreic movements and also to help control hallucinations, delusions, and violent outbursts; fluoxetine, sertraline, nortriptyline, or other compounds may be prescribed for depression. Tranquilizers can help control anxiety and lithium may be prescribed to combat pathological excitement and severe mood swings. However, while medicines may help keep clinical symptoms under control, there is currently no approved treatment to stop or reverse the course of the disease. (Page 5, lines 1-10)

The present invention is directed to a method for treating polyglutamine disorders caused by expanded genomic CAG nucleotides by reducing the availability of free glutamine in astrocytes (page 7, lines 4-6). Glutamine is supplied to neurons by astrocytes via the glutamine-glutamate cycle. Astrocytes are the only cells in the brain rich in glutamine synthetase (page 7, lines 22-23). Reducing the availability of free glutamine prevents or reduces the biosynthesis of toxic proteins (page 7, lines 4-9). The present inventors have found that L-methionine S-sulfoximine, L-ethionine S-sulfoximine, and glufosinate inhibit glutamine synthetase (page 8, lines 5-21) and branched chain α-keto acids derived from leucine, isoleucine or valine reduce the availability of glutamate in the brain thereby reducing the availability of glutamine for the synthesis of polyglutamine proteins (page 8, line 22 to page 9, line 11).

Independent claim 1 is directed to a method for treating a polyglutamine disease (page 7, lines 4-9), comprising administering a compound selected from the group consisting of L-methionine S-sulfoximine, L-ethionine S-sulfoximine, glufosinate and

branched chain α-keto acids derived from leucine, isoleucine or valine (page 1, lines 7-10 and page 7, lines 10-12), to a patient in need of such treatment.

Independent claim 21 is directed to a method for treating a polyglutamine disease caused by expanded genomic CAG nucleotides (page 1, lines 16-21), comprising administering L-methionine S-sulfoximine (page 8, lines 5-16) to a patient suffering from a polyglutamine disease selected from the group consisting of Huntington's disease, spinocerebellar ataxia, and spinobulbar muscular atrophy (page 1, lines 16-23).

VI.

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The only issue on appeal is whether the invention claimed in claims 1-5, 10-11 and 21 is unpatentable under 35 USC §103(a) over Apostolakis et al., *Brain Research Bulletin*, vol. 23, pp. 257-262 (1989); or Ginefri-Gayet et al., *Pharmacology Biochemistry and Behavior*, vol. 43, pp. 173-179 (1992) in view of Liedtke et al. (U.S. Pub. No. 20030013650 A1); further in view of Feurerstein et al. (US Pub. No. 20020173537).

VII.

ARGUMENTS

Claims 1-5, 10-11and 21 are not obvious under 35 USC §103(a) over Apostolakis et al., *Brain Research Bulletin*, vol. 23, pp. 257-262 (1989); or Ginefri-Gayet et al., *Pharmacology Biochemistry and Behavior*, vol. 43, pp. 173-179 (1992) in view of by Liedtke et al. (U.S. Pub. No. 20030013650 A1); further in view of Feurerstein et al. (US Pub. No. 20020173537) because claims 1-5, 10-11 and 21 recite subject matter not disclosed by the cited prior art.

As discussed in the Appeal Brief filed on February 13, 2009, though Apostolakis indicates that MSO suppresses the formation of glutamine and glutamate, Apostolakis also discloses that MSO is a centrally acting neurotoxin with convulsive properties. Contrary to statements made on page 7 of the February 18, 2010 Office Action, Apostolakis does **NOT** disclose the use of MSO for the **treatment** of epilepsy. Apostolakis uses MSO as "a tool for the experimental study of epilepsy" (page 257, left column). Apostolakis uses MSO to induce seizures in order to investigate "a possible correlation of the probability of occurrence of a seizure with the power spectrum characteristics of the interictal EEG in the rabbit" (page 257, left column).

MPEP § 2143.03(VI) states that "[a] prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention." Thus, where a reference teaches away from a claimed feature, the cited art is not available for the purposes of an obviousness rejection. In the instant case, Apostolakis not only fails to teach or suggest MSO as a treatment for polyglutamine diseases but actually teaches away from such a use by disclosing the serious side effects resulting from the administration of MSO in rabbits. Apostolakis teaches that MSO can cause seizures, deformation, atrophy, loss of striation of muscle fibers, fibrosis and degeneration of Purkinje cells in the cerebellum. Apostolakis states on page 257, left column, that "all animals subjected to MSO treatment showed severe hind leg gait disturbances which in most animals so treated (12 out of 14 by the time of this report) deteriorated to the point that lower limb rigid paralysis set in (myopathy with histological findings resembling myositits)". Page 259, left column, under results,

indicates that "[F]ollowing the IV MSO administration the animals became hyperactive and exhibited increased hind leg muscle tonus at 2 hr; at 4-5 hr tetanus-like seizures started". Page 260, right column, states that "muscle lesions are also caused by the IVT MSO administration". Apostolakis concludes that administration of MSO to rabbits in addition to the known convulsive effects may also be responsible for hind leg myopathy. Therefore, Apostolakis explicitly teaches away from using MSO as a therapeutic treatment for any diseases. Because Apostolakis does not suggest or disclose that MSO can be used to treat polyglutamine diseases such as Huntington's disease, spinocerebellar ataxia, and spinobulbar muscular atrophy and in view of the undesirable and serious side effects discussed in Apostolakis (i.e. convulsions, deformation, atrophy, loss of striation of muscle fibers, fibrosis and degeneration of Purkinje cells in the cerebellum) one skilled in the art would not be motivated to modify Apostolakis or combine Apostolakis with the other cited art in an effort to arrive at the presently claimed invention. Applicants point out that a reference must be considered for all that it discloses and that it is improper to combine references where the references teach away from their combination. *In re Grasselli*, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983) (MPEP §2145 paragraph X D 2).

As discussed above, one would not combine Apostolakis with the other cited prior art to arrive at the present invention because Apostolakis teaches away from the presently claimed invention. However, even if the cited references were combined, the combination does not suggest the presently claimed invention. Ginefri-Gayet discloses that MSO, when administered at a convulsant dose (100-200 mg/kg body weight

administered intraperitonealy or 50-75 µg per rat administered by ICV injection) also induces a decrease in body temperature. Ginefri-Gayet states on page 178, right column that "[I]njection of MSO into the third ventricle, allowing the drug to interact more directly not only with thermoregulatory centers in the hypothalamus but also with brainstem and midbrain neuronal structures, led to a rapid decrease of body temperature, reaching its maximum value during the course of the 0200-0230 h period following administration of MSO". Thus, Ginefri-Gayet discloses that MSO elicits hypothermia at a dose of 50-75 µg per rat, which induces convulsions. Ginefri-Gayet also indicates that MSO elicited a time dependent regional perturbation of 5-HT metabolism which could be due to the marked rise in ammonia levels caused by the irreversible inhibition of the activity of glutamine synthetase. Ginefri-Gayet not suggest or disclose that the serious side effects disclosed in Apostolakis can be avoided and Ginefri-Gayet indicates that other undesirable side effects also occur (methionine sulfoximine induced hypothermia). Thus, the combination of the two main references, Ginefri-Gayet and Apostolakis, teaches away from the presently claimed invention that MSO can be used to treat polyglutamine diseases such as Huntington's disease, spinocerebellar ataxia, or spinobulbar muscular atrophy and in view of the undesirable side effects.

Liedtke is directed to an ion channel VR-OAC and does not suggest or disclose that the side effects of MSO administration as presented in Apostolakis and Ginefri-Gayet can be avoided. The only mention of MSO in Liedtke is in paragraph 207 which discusses mammalian expression vectors such as a glutamine synthetase/ methionine

sulfoximine co-amplification vector such as pEE14. There is no suggestion or disclosure regarding the administration of MSO for treating a polyglutamine disease. The office action states on page 4 that Liedtke teaches a glutamine synthetase/methionine sulfoximine co-amplification vector which reads on claims 10 and 11. Applicants are unclear as to how this is related to the present claims as mammalian expression vectors are not part of the present invention nor are they mentioned in claims 10 and 11. In any case. Liedtke does not cure the deficiencies in Apostalakis and Ginefri-Gayet as Liedtke does not suggest or disclose that MSO can be used to treat polyglutamine diseases such as Huntington's disease, spinocerebellar ataxia, or spinobulbar muscular atrophy or suggest that the undesirable side effects disclosed in Apostalakis and Ginefri-Gayet can be overcome.

Feurerstein is directed to a method for treating a polyglutamine disorder using 2-pyrrolidinone derivatives. Feurerstein does not teach the use of MSO and thus does not cure the deficiencies in Apostalakis, Ginefri-Gayet and Liedtke as discussed above. If one skilled in the art combined the disclosures of Apostalakis, Ginefri-Gayet, Liedtke and Feurerstein, they would conclude that the administration of MSO leads to undesirable side effects such as deformation, atrophy, loss of striation of muscle fibers, fibrosis, degeneration of Purkinje cells in the cerebellum, decrease in body temperature, and regional perturbation of 5-HT metabolism which could be due to the marked rise in ammonia levels caused by the irreversible inhibition of the activity of glutamine synthetase, which teaches away from the use of MSO to treat diseases. None of the cited references alone or in combination suggest that MSO can be used to treat

polyglutamine diseases such as Huntington's disease, spinocerebellar ataxia, or spinobulbar muscular atrophy and in view of the side effects disclosed in the prior art, one skilled in the art would not be motivated to test MSO for the treatment of such diseases.

The applicant respectfully points out that the present claims are directed to a method for treating a polyglutamine disease which is not disclosed or suggested by the cited prior art individually or in combination. The composition and kit claims were withdrawn from consideration in view of applicant's election of group I for examination in the present application and are not involved in this appeal.

In summary, Applicants contend that Liedtke and Feurerstein do not suggest or disclose the therapeutic use of MSO and Apostolakis and Ginefri-Gayet actually teach away from using MSO as a treatment for polyglutamine diseases as in the present invention. In view of the numerous undesired effects caused by MSO (convulsant, neurotoxin, etc.) discussed in the cited prior art, applicants contend that the combination of cited prior art does not suggest or disclose administering MSO to any patients for any therapeutic purposes. Therefore, applicants contend that the combination of cited references does not suggest or disclose a method for treating a polyglutamine disease, comprising administering a compound selected from the group consisting of L-methionine S-sulfoximine, L-ethionine S-sulfoximine, glufosinate and branched chain α-keto acids derived from leucine, isoleucine or valine as in the present claims.

Conclusion

For all of the above noted reasons, it is strongly contended that certain clear differences exist between the present invention as claimed in claims 1- 5, 10-11 and 21 and the prior art relied upon by the Examiner. It is further contended that these differences are more than sufficient evidence that the present invention is patentable over the combination of cited prior art.

This final rejection being in error, therefore, it is respectfully requested that this honorable Board of Patent Appeals and Interferences reverse the Examiner's decision in this case and indicate the allowability of claims 1-5, 10-11 and 21.

In the event that this paper is not being timely filed, the Patent Owner respectfully petitions for an appropriate extension of time. Please charge any fee or credit any overpayment pursuant to 37 §C.F.R. 1.16 or §1.17 to Deposit Account No. 02-2135.

Respectfully submitted,

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VIII.

APPENDIX OF CLAIMS ON APPEAL

1. A method for treating a polyglutamine disease, comprising administering a compound selected from the group consisting of L-methionine S-sulfoximine, L-ethionine S-sulfoximine, glufosinate and branched chain α-keto acids derived from leucine, isoleucine or valine, to a patient in need of such treatment.

2. The method according to claim 1, wherein said polyglutamine disease is selected from the group consisting of Huntington's disease, spinocerebellar ataxia, and spinobulbar muscular atrophy.

3. The method according to claim 1, wherein said compound is L-methionine S-sulfoximine or L-ethionine S-sulfoximine administered orally, intravenously, or intrathecally.

4. The method according to claim 1, wherein said L-methionine S-sulfoximine or L-ethionine S-sulfoximine is administered intrathecally at a dosage between 1.0-5.0 mg/kg per 6-10 days.

5. The method according to claim 1, wherein said L-methionine S-sulfoximine or L-ethionine S-sulfoximine is administered orally or intravenously at a dose between 2.0-

10.0 mg/kg per 6-10 days.

Claims 6-9 were withdrawn and are not involved in this appeal.

10. The method according to claim 1, further comprising administering a second compound which inhibits aggregate formation, inhibits transglutaminase, inhibits caspase, or is neuroprotective.

11. The method according to claim 10, wherein said second compound is selected from the group consisting of Congo red, cystamine, cysteamine, minocycline, ethyl eicosapentaenoate, and riluzole.

Claims 12-20 were withdrawn and are not involved in this appeal.

21. A method for treating a polyglutamine disease caused by expanded genomic CAG nucleotides, comprising administering L-methionine S-sulfoximine to a patient suffering from a polyglutamine disease is selected from the group consisting of Huntington's disease, spinocerebellar ataxia, and spinobulbar muscular atrophy.

IX.

Evidence Appendix

None

X.

RELATED PROCEEDINGS APPENDIX

None